The Anti Phospholipid Syndrome

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The anti phospholipid syndrome is a prothrombotic disorder that can affect both the venous and arterial circulations.\textsuperscript{1,2} The deep veins of the lower limbs and the cerebral arterial circulation are the most common sites of venous and arterial thrombosis, respectively.\textsuperscript{2} However, any tissue or organ vascular bed can be affected. Catastrophic antiphospholipid syndrome, which is characterized by clots in multiple small vascular beds and leads to multiorgan failure with high mortality, develops in a small subgroup of patients.\textsuperscript{2,3} In situations in which histopathological confirmation is sought, thrombosis should be present without evidence of inflammation in the vessel wall.\textsuperscript{1}

The other major clinical manifestations of the antiphospholipid syndrome are obstetrical. They include the unexplained death of one or more morphologically normal fetuses at or beyond the 10th week of gestation, the premature birth of one or more morphologically normal neonates before the 34th week of gestation because of either eclampsia or severe preeclampsia, and three or more unexplained, consecutive spontaneous abortions before the 10th week of gestation.\textsuperscript{1}

The revised classification criteria for the antiphospholipid syndrome (2006) emphasize the presence of specific autoantibodies as an essential component of the diagnosis.\textsuperscript{1} The persistence (for >12 weeks) of high titer of autoantibodies of the IgG or IgM isotype, detected by enzyme-linked immunosorbent assay (ELISA) for anti-\(\beta_2\)-glycoprotein I or anticardiolipin antibodies or by lupus-anticoagulant assays, is required.\textsuperscript{1} The lupus-anticoagulant assays detect autoantibodies that have the ability to prolong clotting time in vitro. Such antibodies target \(\beta_2\)-glycoprotein I and prothrombin, both of which are plasma proteins that bind to anionic phospholipids.\textsuperscript{4-6} The term “antiphospholipid antibodies” is often used to encompass any or all of the antibodies detected by ELISA and the lupus-anticoagulant assays. A diagnosis of the antiphospholipid syndrome is made if at least one of the above clinical criteria and one of the laboratory criteria are met.\textsuperscript{1}

\textbf{Role of Autoantibodies with Lupus-Anticoagulant Activity}

A positive test for lupus anticoagulant is a stronger risk factor for thrombosis and adverse pregnancy outcomes after 12 weeks of gestation than positivity for either anti-\(\beta_2\)-glycoprotein I or anticardiolipin antibodies.\textsuperscript{7-9} A case–control study designed to estimate the contribution of genetic and acquired risk factors to a first episode of venous thrombosis in the general population of persons younger than 70 years of age (with no known cancer) showed that 3.1% of persons with venous thrombosis were positive for lupus anticoagulant, as compared with 0.9% of controls (odds
Table 1. Proposed Pathogenetic Mechanisms in the Antiphospholipid Syndrome (APS), Supporting Evidence from Studies in Humans and Animals, and Implications for Targeted Therapy.*

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<td>Increased oxidative stress</td>
<td>Levels of oxidized β2GPI were increased in patients with APS; paraoxonase activity was decreased; lipid peroxidation byproducts were increased; monocytes from patients with APS showed an increase in intracellular ROS.</td>
<td>Free thiol form of β2GPI protects endothelium from ROS; antiphospholipid antibodies promote an increase in intracellular ROS.</td>
<td>ROS contribute to the pathogenesis of murine thrombosis</td>
<td>NAC inhibits ROS-mediated thrombosis; coenzyme Q inhibits antiphospholipid antibody-mediated ROS generation.</td>
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<td>Impaired function of eNOS</td>
<td>Patients with APS had impaired endothelial nitric oxide–dependent vascular relaxation and decreased plasma nitrite levels.</td>
<td>HDL cholesterol from women with antiphospholipid antibodies inhibits endothelial nitric oxide production.</td>
<td>Mice deficient in eNOS do not have a antiphospholipid antibody–mediated potential of thrombosis.</td>
<td>Statins up-regulate eNOS activity (which may account for their protective effect in vitro and in vivo murine model of APS).</td>
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<td>Activation of receptors by anti-β2GPI antibodies</td>
<td>Anti-β2GPI antibodies (specific for domain I) with lupus-anticoagulant activity strongly correlate with thrombosis associated with APS.</td>
<td>The relevant target receptors on platelets are ApoE receptor 2 and glycoprotein Ibα; on monocytes, annexin A2, TLR2, TLR4, and TLR4(A2,43,44); and on endothelial cells, annexin A2, TLR2, and TLR4.</td>
<td>ApoE receptor 2–knockout mice, annexin A2–knockout mice, LPS-insensitive mice are protected from antiphospholipid antibody–mediated thrombosis.</td>
<td>A1 analogues of ApoE receptor 2 and synthetic domain I inhibit anti-β2GPI–mediated effects in vitro and in vivo; NAC inhibits thrombosis associated with TTP in a murine model.</td>
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<td>Increased expression and activation of tissue factor</td>
<td>Increased expression of tissue factor shown in patients with APS.</td>
<td>Up-regulation of tissue factor by antiphospholipid antibodies has been shown in monocytes and neutrophils and on endothelial cells.</td>
<td>Tissue factor plays a role in APS-associated thrombotic microangiopathy.</td>
<td>PDI inhibitors attenuate murine thrombosis; statins inhibited thrombosis in a murine model of tissue factor–dependent APS.</td>
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<td>Increase in free thiol form of factor XI</td>
<td>Patients with APS have elevated levels of the free thiol form of factor XI.</td>
<td>PDI-treated or thioredoxin–treated factor XI is more rapidly converted to factor XIa.</td>
<td>Factor XI plays a critical role in pathologic thrombus formation.</td>
<td>PDI inhibitors and factor XI inhibitors attenuate in vivo thrombus formation in mice and primates.</td>
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<td>Disruption of the annexin A5 shield</td>
<td>Annexin A5 resistance anticoagulant activity correlates with clinical APS.</td>
<td>Decrease in annexin A5 shown in antiphospholipid antibody–treated endothelial cells.</td>
<td>Hydroxychloroquine inhibits anti-β2GPI disruption of the annexin A5 shield in vitro and attenuates thrombosis associated with APS in mice.</td>
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<td>Antibody-mediated activation of complement C3 and C5</td>
<td>Excessive complement activation shown in placentas of patients who are positive for antiphospholipid antibodies, as compared with healthy controls.</td>
<td>C5a binds and activates neutrophils, inducing up-regulation of tissue factor.</td>
<td>Complement has a mediating role in models of thrombosis and fatal loss in murine APS.</td>
<td>C5 inhibitor eculizumab ameliorates catastrophic APS.</td>
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In a case–control study focusing on risk factors for stroke in women in the general population younger than 50 years of age, 17% of the patients with stroke were positive for lupus anticoagulant, as compared with 0.7% of controls (odds ratio, 43.1). The risk was further increased by taking oral contraceptive pills (odds ratio, 201.0) or smoking (odds ratio, 87.0). Approximately 1% of women trying to get pregnant have recurrent miscarriages; of these women, approximately 10 to 15% are estimated to have obstetrical antiphospholipid syndrome. Positivity for lupus anticoagulant is the strongest predictor of subsequent thrombosis in purely obstetrical antiphospholipid syndrome; the annual incidence of deep-vein thrombosis is 1.46%, and the annual incidence of stroke is 0.32%.

Lupus anticoagulant due to anti–β2-glycoprotein I autoantibodies correlates more strongly with a risk of thrombosis than does lupus anticoagulant due to antiprothrombin autoantibodies. The risk of a first thrombotic event among asymptomatic persons who are positive for lupus anticoagulant, anticardiolipin antibodies, and anti–β2-glycoprotein I antibodies — so-called triple-positive patients — is 5.3% per year. These patients have high titers of autoantibodies that bind the major B-cell epitope on domain I of the β2-glycoprotein I molecule. Domain I anti–β2-glycoprotein I autoantibodies confer lupus-anticoagulant activity associated with the highest risk of thrombosis. Assays that detect autoantibodies to the phosphatidylerserine–prothrombin complex (in contrast to prothrombin alone) may help establish the diagnosis of the antiphospholipid syndrome and the associated level of risk, in conjunction with the lupus-anticoagulant assays and the ELISA for anti–β2-glycoprotein I antibodies. The usefulness of also performing the ELISA for anticardiolipin antibodies to diagnose thrombotic antiphospholipid syndrome is being debated.

Autoantibodies from patients with the antiphospholipid syndrome potentiate thrombus formation when infused into mice in which the blood vessel has been injured. The thrombogenic properties are eliminated when the fraction of anti–β2-glycoprotein I autoantibodies is removed. We review the mechanisms that may contribute to thrombosis in the syndrome, integrating clinical biomarker data, results of in vitro mechanistic studies, and relevant animal models (Table 1).
The amino-terminal end of the protein.

Figure 1. Schematic Representation of the Crystal Structure (Fishhook Configuration) of β₂-Glycoprotein I (β2GPI).

The carboxy-terminal amino acid cysteine (Cys) 326 forms a disulfide (S–S) bridge with Cys288. D denotes domain, K lysine, R arginine, and SH free thiol. The numbers indicate the position of the amino acid starting from the amino-terminal end of the protein.

**THROMBOTIC MECHANISMS**

**POST-TRANSLATIONAL REDOX MODIFICATIONS OF β₂-GLYCOPROTEIN I**

A number of findings suggest that the antiphospholipid syndrome is characterized by increased oxidative stress. Paraoxonase activity, which accounts for the antioxidant properties of high-density lipoprotein cholesterol (preventing oxidation of low-density lipoprotein [LDL] cholesterol), is significantly decreased in persons with the syndrome, whereas levels of 8-epi-prostaglandin F₂₀, a biomarker of lipid peroxidation, are elevated. Plasma levels of β₂-glycoprotein I–oxidized LDL complexes are elevated in persons with the antiphospholipid syndrome as compared with healthy controls.

Oxidative stress plays a direct role in the structure and function of β₂-glycoprotein I in patients with the antiphospholipid syndrome. Purified β₂-glycoprotein I is composed of four domains (domains I through IV) that contain two disulfide bridges each and a fifth domain (domain V) that contains an extra disulfide bridge linking cysteine (Cys) 288 with Cys326 (Fig. 1). In healthy persons, the free thiol form of β₂-glycoprotein I predominates in the plasma, characterized by a broken disulfide bridge at Cys32 and Cys60 and another at Cys288 and Cys326. The former pair of free thiols are near the antiphospholipid syndrome B-cell epitope in domain I, and the latter are near the T-cell epitope in domain V. The disulfide bridges at these locations are broken by the oxidoreductases thioredoxin-1 and protein disulfide isomerase (PDI). Under conditions of oxidative stress, disulfide bonds form at these sites.

The relative proportion of plasma β₂-glycoprotein I in the oxidized versus the free thiol form was significantly greater in patients with the antiphospholipid syndrome than in patients with autoimmune disease with or without persistent antiphospholipid antibodies but without the antiphospholipid syndrome, patients with vascular thrombosis without antiphospholipid antibodies, and healthy volunteers (P<0.001 for all comparisons). Patients with the syndrome who were positive for both lupus anticoagulant and anti–β₂-glycoprotein I antibodies had significantly higher levels of oxidized β₂-glycoprotein I than patients who were positive for anti-β₂-glycoprotein I antibodies alone.

Supporting the notion that oxidation unmasks the critical antiphospholipid syndrome B-cell epitope, anti–β₂-glycoprotein I antibodies purified from mice and rabbits that had been immunized with β₂-glycoprotein I displayed decreased binding to oxidoreductase-treated β₂-glycoprotein I, as did autoantibodies that were affinity-purified from patients with the antiphospholipid syndrome (Fig. 2).

**CONFORMATIONS OF β₂-GLYCOPROTEIN I**

β₂-glycoprotein I can potentially exist in a circular form, with domain I interacting with domain V. In this form, the critical B-cell epitope is hidden from the immune system. On binding to an anionic phospholipid surface through domain V, the circular form of β₂-glycoprotein I opens up to a fishhook configuration, exposing the domain I epitope and allowing domain I autoantibodies to bind. The presence of the circular form has yet to be directly shown in
human plasma; however, circumstantial evidence points to its in vivo presence. Domain I anti-β₂GPI glycoprotein I autoantibodies were induced in mice in which protein H (derived from *Streptococcus pyogenes*) was administered. Protein H changes the conformation of β₂GPI from the circular to the theoretically more immunogenic open form in vitro. The relationship of the circular form of β₂GPI to the free thiol form has not been determined.

**TRIGGERS OF THROMBOSIS**

The “two hit” model of thrombosis associated with the antiphospholipid syndrome proposes that an initiating “first hit” injury disrupts the endothelium, and a “second hit” potentiates thrombus formation. Autoantibodies from patients with the antiphospholipid syndrome that are infused into mice do not promote thrombus formation in the absence of vessel-wall injury. A key step in allowing β₂GPI immune complexes to form on the cell surface is endothelial-cell priming. β₂GPI does not bind unstimulated endothelium in vivo. In catastrophic antiphospholipid syndrome, infection and recent surgery are recognized precipitants of endothelial injury. However, the initiating stimulus is not identified in most cases of thrombotic antiphospholipid syndrome. We postulate that disturbance of the redox balance in the vascular milieu in patients with the antiphospholipid syndrome may constitute a substantial first hit that primes the endothelium, allowing β₂GPI immune complexes to form on the cell surface and assert their pathogenicity.

Patients with the antiphospholipid syndrome have significantly lower levels of the endothelium-protective free thiol form of β₂GPI that provides a buffer against oxidative stress than do healthy persons. The odds ratio for reduced levels of the free thiol form of β₂GPI in patients with the antiphospholipid syndrome, as compared with age-matched and sex-matched controls, was reported to be 4.1 (95% confidence interval [CI], 1.9 to 8.8). Oxidative stress from exogenous sources such as smoking may tip the vascular endothelial milieu toward a prothrombotic phenotype. For example, oxidative stress can up-regulate the expression of annexin A2, an endothelial cell-surface receptor for β₂GPI that has an important role in the pathogenesis of the antiphospholipid syndrome. Among young women, the odds ratio for ischemic stroke in the presence of lupus anticoagulant is 43.1, and it increases to 87.0 with concurrent oxidative stress (and other pathophysiological disturbances) induced by smoking. In a murine model of thrombosis, reactive oxygen species induced platelet aggregation, endothelial-cell stimulation, and expression of von Willebrand factor. N-acetylcysteine (NAC), a scavenger of reactive oxygen species, inhibited thrombus formation in this model. The therapeutic value of NAC in the antiphospholipid syndrome may be worth exploring (Fig. 3).

**ENDOTHELIAL NITRIC OXIDE SYNTHASE**

Patients with the antiphospholipid syndrome have decreased levels of plasma nitrite, as compared with controls. They also have impaired endothelium-dependent vascular responses, which suggests that the activity of endothelial nitric oxide synthase is abnormal.

Endothelium-derived nitric oxide plays an im-
important role in healthy endothelial function.\textsuperscript{84-86} It is produced by enzymatic conversion of L-arginine by endothelial nitric oxide synthase.\textsuperscript{87} Reduced expression and activity of endothelial nitric oxide synthase can result in the generation of superoxide and peroxynitrite.\textsuperscript{88} Because nitric oxide has an exceptionally short half-life, the activity of endothelial nitric oxide synthase is estimated by measuring nitric oxide metabolites in plasma. Plasma nitrite most closely reflects changes in the activity of endothelial nitric oxide synthase in humans.\textsuperscript{89}

In a murine model, domain I anti–β\textsubscript{2}-glycoprotein I autoantibodies decreased bioavailable nitric oxide by antagonizing the activity of endothelial nitric oxide synthase, which led to monocytosis adhesion to the endothelium.\textsuperscript{33} The autoantibodies exerted their pathogenic effects in this model in a manner that was independent of complement and Fc receptor.\textsuperscript{33} Endothelial nitric oxide–dependent arterial relaxation was inhibited by domain I anti–β\textsubscript{2}-glycoprotein I autoantibodies in these mice,\textsuperscript{33} reflecting vascular disturbances analogous to those in humans with antiphospholipid autoantibodies.\textsuperscript{27} Inhibition of the activity of endothelial nitric oxide synthase was mediated by the F(ab\textsuperscript{'})\textsubscript{2} portion of domain I anti–β\textsubscript{2}-glycoprotein I autoantibodies, which dimerized β\textsubscript{2}glycoprotein I molecules attached to apolipoprotein E (ApoE) receptor 2 (LDL receptor–related protein 8), cross-linking and activating ApoE receptor 2.\textsuperscript{33} Anti–β\textsubscript{2}-glycoprotein I autoantibodies did not enhance leukocyte adhesion to the endothelium, nor did they potentiate in vivo thrombus formation in mice deficient in endothelial nitric oxide synthase or ApoE receptor 2, findings that indicate the critical role of these receptors in pathogenicity mediated by anti–β\textsubscript{2}-glycoprotein I autoantibodies.\textsuperscript{33} Statins — inhibitors of 3-hydroxy-3-methyl-
glutaryl–coenzyme A (HMG-CoA) reductase — block the thrombogenic properties of antiphospholipid autoantibodies in vitro and in vivo. Statins may be protective in the antiphospholipid syndrome owing in part to their up-regulation of endothelial nitric oxide synthase.

A number of strategies are being pursued to disrupt the formation of β2-glycoprotein I immune complexes on cell surfaces. Domain V of β2-glycoprotein I binds the A1 ligand–binding type A module of ApoE receptor 2. A dimeric A1–A1 molecule blocks the formation of β2-glycoprotein I immune complexes on anionic phospholipid surfaces. Mice treated with soluble monomeric A1 are protected from the thrombogenic effects of anti–β2-glycoprotein I autoantibodies, providing proof of principle that A1–A1 dimers have therapeutic value. Infusion of synthetic domain I of β2-glycoprotein I was protective in a murine model of thrombosis induced by anti–β2-glycoprotein I autoantibodies (Fig. 3).

The binding of pathogenic domain I anti–β2-glycoprotein I autoantibodies to β2-glycoprotein I may be inhibited by breaking the disulfide bond and inducing free thiol formation at Cys32 and Cys60 within domain I of β2-glycoprotein I (Fig. 3). NAC is able to break an analogous disulfide bond within von Willebrand factor, with implications for treating patients with thrombotic thrombocytopenic purpura, and exploration of its therapeutic potential in the antiphospholipid syndrome may be of value (Fig. 3).

**ENDOTHELIAL CELLS AND MONOCYTES**

Antiphospholipid autoantibodies may up-regulate the cell-surface expression of proadhesive and procoagulant molecules such as tissue factor. Anti–β2-glycoprotein I autoantibodies may induce signaling by means of a multiprotein complex on the endothelial cell surface that includes annexin A2 (bound by β2-glycoprotein I), toll-like receptor 4 (TLR4), calreticulin, and nucleolin. Intracellular activation downstream of TLR4 occurs through myeloid differentiation factor 88, culminating in activation of nuclear factor κB (NF-κB). The targeting of NF-κB is a therapeutic option. The absence of annexin A2 was reported to protect mice against the prothrombotic effects of infused autoantibodies from patients with the antiphospholipid syndrome. Mice with resistance to lipopolysaccharide were also protected, a finding that supports the relevance of TLR4 in the pathogenesis of the antiphospholipid syndrome.

β2-glycoprotein I has been shown to colocalize with annexin A2 and TLR4 on the lipid rafts of monocytes. Anti–β2-glycoprotein I autoantibodies stimulate monocytes to increase tissue factor expression and release tumor necrosis factor α (TNF-α). Statins may be protective in the antiphospholipid syndrome as compared with monocyte dysfunction induced through undefined indirect pathways. In one study, 19 of 32 affinity-purified antibodies from patients with the antiphospholipid syndrome were shown to induce activation of human monocytes and endothelial cells. However, in that series of experiments, the results showed that activation occurred through toll-like receptor 2 (TLR2) and CD14, not TLR4. Further work is needed to resolve these discrepancies.

Autoantibodies from patients with the antiphospholipid syndrome can disrupt the mitochondrial function of monocytes and neutrophils, leading to the generation of various intracellular reactive oxygen species and the subsequent expression of tissue factor. Antibodies from patients with the syndrome do not colocalize with mitochondria, suggesting that mitochondrial dysfunction is induced through undefined indirect pathways. In another study, the inhibition of intracellular reactive oxygen species in monocytes with the use of NAC, vitamin C, or mitochondrial cofactor coenzyme Q10 prevented the up-regulation of tissue factor induced by antiphospholipid autoantibodies (Fig. 3).

Human monocytes are activated in a distinct manner by polyclonal autoantibodies derived from patients with purely thrombotic antiphospholipid syndrome as compared with monocyte activation by autoantibodies from patients with obstetrical antiphospholipid syndrome. Autoantibodies from patients with thrombotic antiphospholipid syndrome induce tissue factor expression, which is caused by the autoantibody fraction that binds β2-glycoprotein I.

**TISSUE FACTOR**

Tissue factor is the key initiator of the extrinsic coagulation pathway. It is located on cell surfaces and microparticles in an encrypted, inactive form. On vessel injury leading to exposure...
of phosphatidylserine, tissue factor becomes de-encrypted and activated, enabling it to bind factor VIIa, which leads to activation of factor IX and factor X.52 The relevance of tissue factor in the pathogenesis of the antiphospholipid syndrome is supported by the results of in vitro and in vivo murine studies.50,54 Thiol exchange reactions play an important role in the regulation of tissue factor from the encrypted to the de-encrypted form.92 PDI, an extracellular regulator of thiol exchange, is associated with cell-surface tissue factor and is required for tissue factor-dependent thrombosis in vivo.92 Hence, PDI inhibitors95 may therapeutically target tissue factor in the pathogenesis of the antiphospholipid syndrome (Fig. 3).

**FACTOR XI**

Elevated levels of coagulation factor XI confer a predisposition to venous thrombosis93 and stroke94 in the general population, mirroring the distribution of thrombosis in patients with the antiphospholipid syndrome. A link has been discovered between the antiphospholipid syndrome and dysregulated activation of factor XI.56 Factor XI is a proenzyme that is cleaved to its active form (factor XIa) by factor XIIa or thrombin.95 Factor XIa is responsible for factor IX activation, ultimately leading to a burst of thrombin generation.95 Factor XI can be a substrate of the oxidoreductases thioredoxin 1 and PDI,96 which target the factor XI intrachain disulfide bonds at Cys118–Cys147 and Cys362–Cys482 and the interchain disulfide bond Cys321–Cys321, generating free thiols at these positions.56 Both the free thiol form and the intact disulfide-bridge form of factor XI are found in human plasma.56 In one study, patients with the antiphospholipid syndrome had significantly higher levels of the free thiol form of factor XI than age-matched and sex-matched controls.56 Oxidoreductase-treated factor XI was more rapidly converted to factor XIa by factor XIIa and thrombin than was the untreated form. The interaction between factor XI and PDI in the context of thrombosis associated with the antiphospholipid syndrome warrants further exploration. Inhibitors of PDI and factor XIa are effective in treating thrombosis in animal models95,96 (Fig. 3). Inhibition of factor XI provides protection against thrombosis but is not associated with an increased risk of bleeding in these models, making factor XI an attractive therapeutic target.57

The Cys362–Cys482 free thiols may not be critical for the potentiation of factor XI activation. Mutagenesis of Cys362 and Cys482 to alanine, which eliminates the disulfide bridge between the heavy chain and light chain of factor XI, leads to decreased ligation of factor IX by the factor XIa mutants.97

**PLATELETS**

β₂-glycoprotein I can interact with the von Willebrand factor receptor glycoprotein Ibα37,38 and ApoE receptor 2.37 This enables anti-β₂-glycoprotein I autoantibodies to cross-link these receptors, leading to potentiation of platelet activation, the release of thromboxane A₂, and an increase in platelet adhesiveness.37,38 Platelet factor 4, a cationic protein released by activated platelets, can facilitate the dimerization of β₂-glycoprotein I, enhancing the formation of pathogenic immune complexes on the platelet surface.98

**ANNEXIN A5 ANTIICOAGULANT SHIELD AND HYDROXYCHLOROQUINE**

In one model of the pathogenesis of the antiphospholipid syndrome, annexin A5 binds to phosphatidylserine surfaces, forming a shield that inhibits the formation of procoagulant complexes.58 An in vitro study has shown that domain I anti-β₂-glycoprotein I autoantibodies in complex with β₂-glycoprotein I can disrupt the shield, exposing procoagulant phosphatidylserine and hence predisposing to thrombosis.99 Hydroxychloroquine inhibits the ability of β₂-glycoprotein I immune complexes to disrupt the annexin A5 matrix on the endothelial-cell surface59 (Fig. 3). Hydroxychloroquine diminished antiphospholipid autoantibody–mediated thrombosis in vivo in a murine model.60

**COMPLEMENT AND NEUTROPHILS**

Case reports document the use of the C5 inhibitor eculizumab to prevent antiphospholipid syndrome–associated thrombotic microangiopathy that complicates renal transplantation,62 and to treat patients with acute catastrophic antiphospholipid syndrome65 (Fig. 3). In vivo murine studies implicating the activation of the classical complement pathway in thrombosis associated with the antiphospholipid syndrome23,64 were the basis for the use of eculizumab in these case reports. Activation of complement by antiphospholipid autoantibodies generates C5a, which binds and activates neutrophils, leading to tissue
factor expression.52 On the basis of murine studies, C3 and C5 have been proposed as possible therapeutic targets for treating obstetrical antiphospholipid syndrome62,63 (Fig. 3).

DISTURBANCE OF INNATE IMMUNITY

The prevalence of lupus-anticoagulant positivity among patients with systemic lupus erythematosus (SLE) is 30%,100 and the presence of lupus-anticoagulant positivity in such patients is associated with an increased risk of thrombosis (odds ratio, 5.6).101 Forty percent of patients with the antiphospholipid syndrome also have SLE,2 and 37% of patients with SLE have anti–β2-glycoprotein I autoantibodies.102 These findings suggest that there is overlap in the pathogenesis of SLE and that of the antiphospholipid syndrome.

A relationship between the two disorders is supported by the spontaneous development of domain I anti–β2-glycoprotein I autoantibodies103 and the development of a syndrome analogous to human antiphospholipid syndrome in a murine model of lupus, NZW x BXSB F1 male mice.67 In this model, a major contributor to pathogenesis is TLR7 duplication resulting from translocation of TLR7 from the X to the Y chromosome in the BXSB male mice.68 Dysregulated activation of TLR7 in plasmacytoid dendritic cells by RNA containing immune complexes and the generation of superoxide.

B-cell activating factor (BAFF) is a cytokine that is crucial for B-cell survival.105 The BAFF-inhibiting antibody belimumab has recently been approved for the treatment of SLE.106 BAFF inhibition prevents thrombosis in NZW x BXSB F1 male mice,71 a finding that suggests it may have a role in the prevention of thrombosis associated with the antiphospholipid syndrome in high-risk patients with SLE.70

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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